

Appl. No. : 09/804,480
Filed : March 12, 2001

REMARKS

No amendments are being made herein. Claims 1-8 remain pending in the application. The Applicants have carefully considered all of the Examiner's rejections and remarks but respectfully submit that the claims are allowable for at least the following reasons.

Rejections under § 103

The Examiner rejected Claims 1-8 under 35 U.S.C. § 103(a) as being unpatentable over Gonzalez et al. (1999) in view of Tung et al. (1992). The Examiner argued that Gonzalez teaches high-throughput screening through electrical stimulation. The Examiner noted that Gonzalez does not teach the claimed biphasic stimulation protocol but argued that Tung does.

A *prima facie* case of obviousness requires that all of the claim limitations are taught or suggested by the prior art. See M.P.E.P. § 2143.03. Claim 1 requires exposing cells to *a series* of biphasic electric fields at *a rate of approximately 20 to 100 pulses per second*. Tung teaches a simulation of biphasic rectangular pulse applied to cardiac muscle cells in order to simulate the effect of such a pulse during electrical defibrillation of the heart. Tung does not teach applying a series of such pulses. Rather, Tung teaches applying only *a single* biphasic pulse. This fact is consistent with the purpose of Tung, which was to investigate pulses for use in defibrillation devices. Such defibrillation pulses are used to return a fibrillating heart back to normal rhythm through a strong electric shock. Biphasic defibrillators do not use a series of approximately 20 to 100 such pulses per second as claimed in the instant application and such a series is not disclosed or suggested in Tung. Gonzalez also does not disclose a series of electric fields at a rate of approximately 20 to 100 pulses. Rather, Gonzalez teaches traditional "voltage clamping" (e.g., using a patch clamp technique with voltage steps). See Gonzales, page 434, column 2 and caption for Figure 2. Gonzalez refers generally to "rapid and repetitive stimulation," however; this statement does not teach applying a series of biphasic pulses at 20 to 100 Hz as recited in the claims. Accordingly, the combination of Gonzalez and Tung does not teach or suggest the required claim limitation of exposing cells to a series of biphasic electric fields at a rate of approximately 20 to 100 pulses per second. As such, the Applicants respectfully submit that a *prima facie* case of obviousness has not been met.

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A *prima facie* case of obviousness also requires that there “be some suggestion or motivation, either in the reference themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings.” M.P.E.P. § 2143. “The mere fact that reference can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination.” M.P.E.P. § 2143.01. “If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification.” *Id.* “If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious.” *Id.*

The Applicants respectfully submit that there is no motivation to combine Gonzalez with Tung. As noted above, Tung is directed to applying biphasic electric pulses for the purpose of defibrillating a heart. Gonzalez is directed to applying electrical stimulation for the purpose of cell-based assays for drug screening. As noted in Tung, the application of the biphasic signals resulted in very similar electrical responses to monophasic signals. *See* Tung, page 377, column 2 to page 378, column 1. Furthermore, as noted in the attached Exhibit A, the benefit of biphasic pulses in defibrillation is that lower energy is required than monophasic pulses. Accordingly, the considerations for choosing biphasic pulses for defibrillation as disclosed in Tung bear no relationship to considerations for changing transmembrane potential in a controlled way for FRET detection. Those of skill in the art would not recognize any feature of the defibrillating biphasic pulses in Tung that would make them suited for application in the very different area of fluorescence based voltage sensing for drug screening. As such, one of skill in the art would not be motivated to combine the teachings of Tung with Gonzalez. For these additional reasons, the Applicants respectfully submit that a *prima facie* case of obviousness has not been met.

CONCLUSION

In contrast to what is disclosed or suggested in any of the prior art currently or previously cited, the Applicants have discovered that “[b]y applying a repetitive train of electrical stimuli, separated by a time interval smaller than the membrane time constant, large sustained membrane

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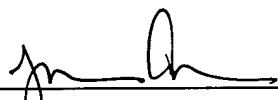
voltage changes can be created.” Specification, page 36, lines 4-5. Thus, in the instant claims, a specific electric field stimulus is provided that “produce[s] a controlled change in transmembrane potential.” The Applicants respectfully submit that they have thus provided a significant and patentable advance over the prior art and request a timely issuance of a Notice of Allowance.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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